SUPPLEMENTARY APPENDIX

A phase 2 study of rituximab, bendamustine, bortezomib and dexamethasone for first-line treatment of older patients with mantle cell lymphoma

Rémy Gressin [1,2] Nicolas Daguindau,[3] Adrian Tempescul,[4] Anne Moreau,[5] Sylvain Carras,[1] Emmanuelle Tchernonog,[6] Anna Schmitt,[7] Roch Houot,[8] Caroline Dartigeas,[9] Jean Michel Pignon,[10] Selim Corm,[11] Anne Banos,[12] Christiane Mounier,[13] Jehan Dupuis,[14] Margaret Macro,[15] Joel Fleury,[16] Fabrice Jardin,[17] Clementine Sarkozy,[18] Ghandi Damaj,[19] Pierre Feugier,[20] Luc Matthieu Fornecker,[21] Cecile Chabrot,[22] Veronique Dorvaux,[23] Krimo Bouadallah,[24] Sandy Amorin,[25] Reda Garidi,[26] Laurent Voillat,[27] Bertrand Joly,[28] Philippe Solal Celigny,[29] Nadine Morineau,[30] Marie Pierre Moles,[31] Hacene Zerazhi,[32] Jean Fontan,[33] Yazid Arkam,[34] Magda Alexis,[35] Vincent Delwail,[36] Jean Pierre Vilque,[37] Loic Ysebaert,[38] Steven Le Gouill,[39] Mary B. Callanan,[2] [40]for the Lymphoma Study Association

[1]Onco-Hematology Department, Grenoble University Hospital; [2]INSERM 1209, CNRS UMR 5309, Faculté de Médecine, Université Grenoble-Alpes, Institute for Advanced Biosciences, Grenoble; [3]Hematology Department, Annecy Hospital; [4]Hematology Department, Brest University Hospital; [5]Pathology Department, Nantes University Hospital; [6]Hematology Department, Montpellier University Hospital; [7]Hematology Department, Cancer Institute Bergonie Bordeaux; [8]Hematology Department, Rennes University Hospital; [9]Hematology Department, Tours University Hospital; [10]Hematology Department, Dunkerque Hospital; [11]Hematology Department, Chambery Hospital; [12]Hematology Department, Bayonne Hospital; [13]Hematology Department, Loire Cancer Institute, Saint Etienne; [14]Lymphoid Malignancies Unit, Henri Mondor University Hospital, Assistance Publique-Hôpitaux de Paris, Créteil; [15]IHBN - Hematology Department, Caen University Hospital; [16]Hematology Department, Clermont-Ferrand Cancer Institute; [17]Hematology Department, Rouen University Hospital; [18]Hematology Department, Hospices Civils de Lyon, Centre Hospitalier Lyon Sud. INSERM 1052; [19]Hematology Department, Amiens University Hospital; [20]Hematology Department, Nancy University Hospital; [21]Hematology Department, University Hospital Strasbourg; [22]Hematology Department, University Clermont-Ferrand Hospital; [23]Hematology Department, Metz University Hospital; [24]Hematology Department, Bordeaux University Hospital; [25]Hematology Department, University Hospital Paris Saint-Louis; [26]Hematology Department, Saint Quentin Hospital; [27]Hematology Department, Chalon Hospital; [28]Hematology Department, Corbeil Hospital; [29]Hematology Department, Victor Hugo Clinic, Le Mans; [30]Hematology Department, Catherine de Sienne Clinic, Nantes; [31]Hematology Department, Angers University Hospital; [32]Hematology Department, Avignon Hospital; [33]Hematology Department, Besançon University Hospital; [34]Hematology Department, Mulhouse Hospital; [35]Hematology Department, Orleans Hospital; [36]Onco-Hematology Department, University Hospital Poitiers and INSERM, CIC 1402, Poitiers University; [37]Hematology Department, Baclesse Caen Cancer Center; [38]Hematology Department, Toulouse University Hospital; [39]Hematology Department, Nantes University Hospital and [40]Unit for Innovation in Genetics and Epigenetics in Oncology, Dijon University Hospital, France

RG, SL and MBC contributed equally to this work.

 doi:10.3324/haematol.2018.191429

Received: February 23, 2018.

Accepted: August 23, 2018.

Pre-published: August 31, 2018.

Correspondence: rgressin@chu-grenoble.fr or mary.callanan@chu-dijon.fr

Supplementary Online Information

A phase 2 study of rituximab, bendamustine, bortezomib and dexamethasone for first line treatment of older patients with mantle cell lymphoma.

Authors:

Rémy Gressin[1,2], Nicolas Daguindau[3], Adrian Tempescul[4], Anne Moreau[5], Sylvain Carras[1], Emmanuelle Tchernonog[6], Anna Schmitt[7], Roch Houot[8], Caroline Dartigeas[9], Jean Michel Pignon[10], Selim Corm[11], Anne Banos[12], Christiane Mounier[13], Jehan Dupuis[14], Margaret Macro[15], Joel Fleury[16], Fabrice Jardin[17], Clemetine Sarkozy[18], Ghandi Damaj[19], Pierre Feugier[20], Luc Matthieu Fornecker[21], Cecile Chabrot[22], Veronique Dorvaux[23], Krimo Bouadallah[24], Sandy Amorin[25], Reda Garidi[26], Laurent Voillat[27], Bertrand Joly[28], Philippe Solal Celigny[29], Nadine Morineau[30], Marie Pierre Moles[31], Hacene Zerazhi[32], Jean Fontan[33], Yazid Arkam[34], Magda Alexis[35], Vincent Delwail[36], Jean Pierre Vilque[37], Loic Ysebaert[38], Steven Le Gouill[39] , Mary B. Callanan[2, 40] for the Lymphoma Study Association.

Authors' affiliations: As in article

Contact information for correspondence:
Rémy Gressin : E-mail, rgressin@chu-grenoble.fr
Mary Callanan : E-mail, mary.callanan@chu-dijon.fr

The following sections are included :

Online Supplementary Methods

RiBVD regimen

A treatment cycle was administered as follows: intravenous (IV) rituximab at 375 mg/m^2 on day 1, IV bendamustine at 90 mg/m^2 on days 1 and 2, sub-cutaneous bortezomib (Velcade®) at 1.3 mg/m^2 on days 1, 4, 8 and 11 and IV Dexamethasone at 40 mg total dose (TD) at day 2 (*Online Supplementary Table S2*). Patients were assessed for response after cycle 4. Responding patients [partial response (PR), CR or complete response unconfirmed (CRu)] received two additional cycles. Maintenance therapy was not performed. If needed, drug doses were adjusted, based on toxicity (*Online Supplementary Table S3*). While primary prophylaxis with valacyclovir was mandatory for prevention of Herpes virus reactivation, there was no recommendation for prevention of Pneumocystis infection.

Response and safety assessments

Deauville scores of 1-3 were considered negative while scores of 4-5 were considered positive. A bone marrow biopsy was performed at diagnosis and if positive was repeated at the end of treatment and thereafter annually. An independent monitoring commission had sole responsibility for continuation or early stopping of the trial, based on assessment of toxicity findings which were reviewed annually. The trial data were collected via internet by the Webtrial software (QuanticSoft©). All data were individually rechecked for accuracy.

Molecular minimal residual disease (MRD)

MRD negativity was defined, at a given time point, as absence of detectable MRD target by qPCR (assay sensitivity of 10-5). When two samples were analyzed at the same time point (paired PB and BM, for example), MRD negativity was defined as absence of detectable MRD target by qPCR in both samples (sensitivity 10-5).

Sample size calculation and statistical Analysis

Predefined secondary study objectives were as follows : to determine the overall and complete response rates according to CT scan and FDG-PET imaging (IWC criteria) after 4 and 6 cycles, respectively[1] ; to assess the prognostic impact on survival of FDG-PET and molecular MRD-based responses in blood and bone marrow; to determine the predictive value of the MIPI.[2] Survival (PFS, OS) was defined according to the international workshop for standardization.[3] Survival probabilities were calculated by the Kaplan-Meier method and compared by the Log Rank test. Probabilities (*P*) of <0.05 were considered significant.

References

1. Cheson BD, Pfistner B, Juweid ME, et al. Revised response criteria for malignant lymphoma. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2007;25(5):579-586.
2. Hoster E, Dreyling M, Klapper W, et al. A new prognostic index (MIPI) for patients with advanced-stage mantle cell lymphoma. Blood. 2008;111(2):558-565.
3. Cheson BD, Horning SJ, Coiffier B, et al. Report of an international workshop to standardize response criteria for non-Hodgkin's lymphomas. NCI Sponsored International Working Group. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 1999;17(4):1244-1253.

Supplementary Table S1. Inclusion and non-inclusion criteria for the RiBVD phase 2 trial.

Summary of inclusion criteria

- Mantle-cell lymphoma WHO 2008 criteria at diagnosis, CD20+
- No prior treatment (patients treated previously with a localized irradiation or a splenectomy could be recruited)
- Patients aged 65 years or more without limit of age
- Patients between 18 and 65 unable or unwilling to receive dose intense therapy
- Ann Arbor Stage II, III, IV
- ECOG status 0, 1 or 2
- Absence of neuro-meningeal involvement
- No previous cancer or in remission for more than 3 years without contra indication for any of the drugs used in the scheme (rituximab, bendamustine, bortezomib or dexamethasone)
- Without cardiac impairment unless lymphoma related
- Biological values as follows or related to lymphoma by bone marrow involvement or hypersplenism or hepatic involvement:
    - Neutrophils ≥ 1 G/L
    - Platelets ≥ 50 G/L
    - SGPT and SGOT and alkaline phosphatases ≤ 4 N
    - Bilirubin < 3 N
    - Creatinine clearance ≥ 20 mL/min
- HIV negative
- Active B or C Hepatitis
- No neuropathy > 2 to the NCI scale
- Who have signed an informed consent

Non Inclusion Criteria

- Other type of lymphoma related to the WHO 2008 classification
- Relapsed patient after one different treatment other than a localized irradiation or a splenectomy
- Central Nervous System localization
- At least one contra-indication of any drugs used in the scheme, rituximab, bendamustine, bortezomib or dexamethasone
- Non-stabilized diabetes
- HIV + or active hepatitis C or B,
- Bad performance status defined as ECOG score ≥ 3,
- Peripheral neuropathy whatever the origin scored ≥ 2 on the NCI scale
- Non-stabilized cardiac insufficiency
- Patients who cannot receive hydration for the treatment or to prevent a tumor lysis syndrome
- Patients who cannot be assigned to regular surveillance
- Patients who have not provided written, informed informed consent

Supplementary information and methods Table S3. RiBVD dose modifications according to toxicity by the NCI-CTCAE scale version.3 (http://ctep.cancer.gov).

1 - Modifications at day 1 of each cycle

The cycle 1 of RiBVD might be realized at full dose

For cycles 2 to 6 recommendations are to be used according to:

1 – hematological toxicities
2 – non-hematological, non-neurological toxicities
3 – neurological toxicities

A missed dose of Bortezomib was not be 'rescued'.

1a - Modifications according to haematological toxicities

No modification, if neutropenia or thrombopenia are caused by lymphoma.
Anemia is never a cause for modification.

Decision Table 1

<table>
<tr><th>Hematological toxicities

(Neutropenia or thrombopenia)</th><th>Delayed next RiBVD cycle</th><th>Bortezomib

dose modification</th><th>Bendamustine

dose modification</th></tr>
<tr><td>Grade 1
Neutrophils =1.5-1.9 G/L

&/or Platelets=75-99 G/L</td><td>no

no</td><td>no

no</td><td>no

no</td></tr>
<tr><td>Grade 2

Neutrophils =1-1.5 G/L

&/or Platelets =50-74 G/L</td><td>no

no</td><td>no

no</td><td>60 mg/m2 D1 and D2

60 mg/m2 D1 and D2</td></tr>
<tr><td rowspan="2">Grade 3[$]

Neutrophils =0.5-1 G/L

&/or Platelets =25-50 G/L</td><td>Yes* until platelets>50 and neutrophils>1</td><td>dose inferior to the previous cycle **</td><td rowspan="2">dose inferior to the previous cycle ***</td></tr>
<tr><td colspan="2">and Lenograstim****</td></tr>
<tr><td rowspan="2">Grade 4[$]

Neutrophils <0.5 G/L

&/or Platelets <25 G/L</td><td>Yes* until platelets>50 and neutrophils>1</td><td>dose inferior to the previous cycle **</td><td rowspan="2">dose inferior of the previous cycle ***</td></tr>
<tr><td colspan="2">and Lenograstim****</td></tr>
</table>

* yes = delay the cycle between 8 days to 15 days if necessary.
** dose inferior to the previous cycle
If the patient received 1.3 mg/m², reduce the Bortezomib dose to 1.0 mg/m²,
If the patient received 1 mg/m², reduce the Bortezomib dose to 0.7 mg/m²,
If the patient received 0.7 mg/m², reduce the Bortezomib dose to 0.5 mg/m²,
If the patient received 0.5mg/m², stop Bortezomib

*** dose inferior to the previous cycle
if 90 mg/m² D1 and D2, reduce the dose of Bendamustine to 60 mg/m² D1 and D2,
if 60 mg/m² D1 and 2, reduce the dose of Bendamustine to 60 mg/m² D1 only,
if 60 mg/m² at D1 only, stop Bendamustine.

**** Initiation of Lenograstim until neutrophils > 1 G/L ; used systematically after each subsequent cycle to prevent neutropenia. Recommendations are to start treatment 24 hours after last injection of the cycle for a minimum of 6 consecutive days and until neutrophil count > 1 G./L.

1b - Modifications according to a non-neurological, non-hematologic toxicity

The maximal grade of toxicity of the previous cycle was considered, and the following instructions provided to investigators.
For grade 3 or 4:
Delay the next cycle until recovery of a grade 0 or 1
Begin with an inferior dose level of Bortezomib and Bendamustine (Decision Table 1, above)

1c - Modifications according to neurological toxicity (NCI-CTCAE scale)

Bortezomib doses were modified according to the following recommendations (overleaf) :

Neuropathic Pain Grades NCI CTCAE		Sensitive Neuropathy (NCI CTCAE Grade)				
		0	**1**	**2**	**3**	**4**
		None	Asymptomatic ; loss of deep tendon reflexes or paresthesia (including tingling) but not interfering with function.	Sensory alteration or paresthesia (including tingling), interfering with function but not with ADL	Sensory alteration or paresthesia interfering with ADL	Disabling
0	none	Same Dose	Same Dose	Reduction ~25%* dose	Stop** then reduction ~50% dose	Stop Bortezomib
1	Asymptomatic weakness on exam/testing only.	Same Dose	Same Dose	reduction ~25%* dose	Stop** then reduction ~50% dose	Stop Bortezomib
2	Symptomatic weakness interfering with function, but not interfering with ADL.	Reduction ~25%* dose	Stop** then reduction ~50% dose	Stop** then reduction ~50% dose	Stop** then reduction ~50% dose	Stop Bortezomib
3	Weakness interfering with ADL; bracing or assistance to walk (e.g; cane or worker)) indicated	Stop** then reduction ~50% dose	Stop** then reduction ~50% dose	Stop** then reduction ~50% dose	Stop Bortezomib	Stop Bortezomib
4	Life threatening ; Disablinb (e.g, paralysis)	Stop Bortezomib	Stop Bortezomib	Stop Bortezomib	Stop Bortezomib	Stop Bortezomib

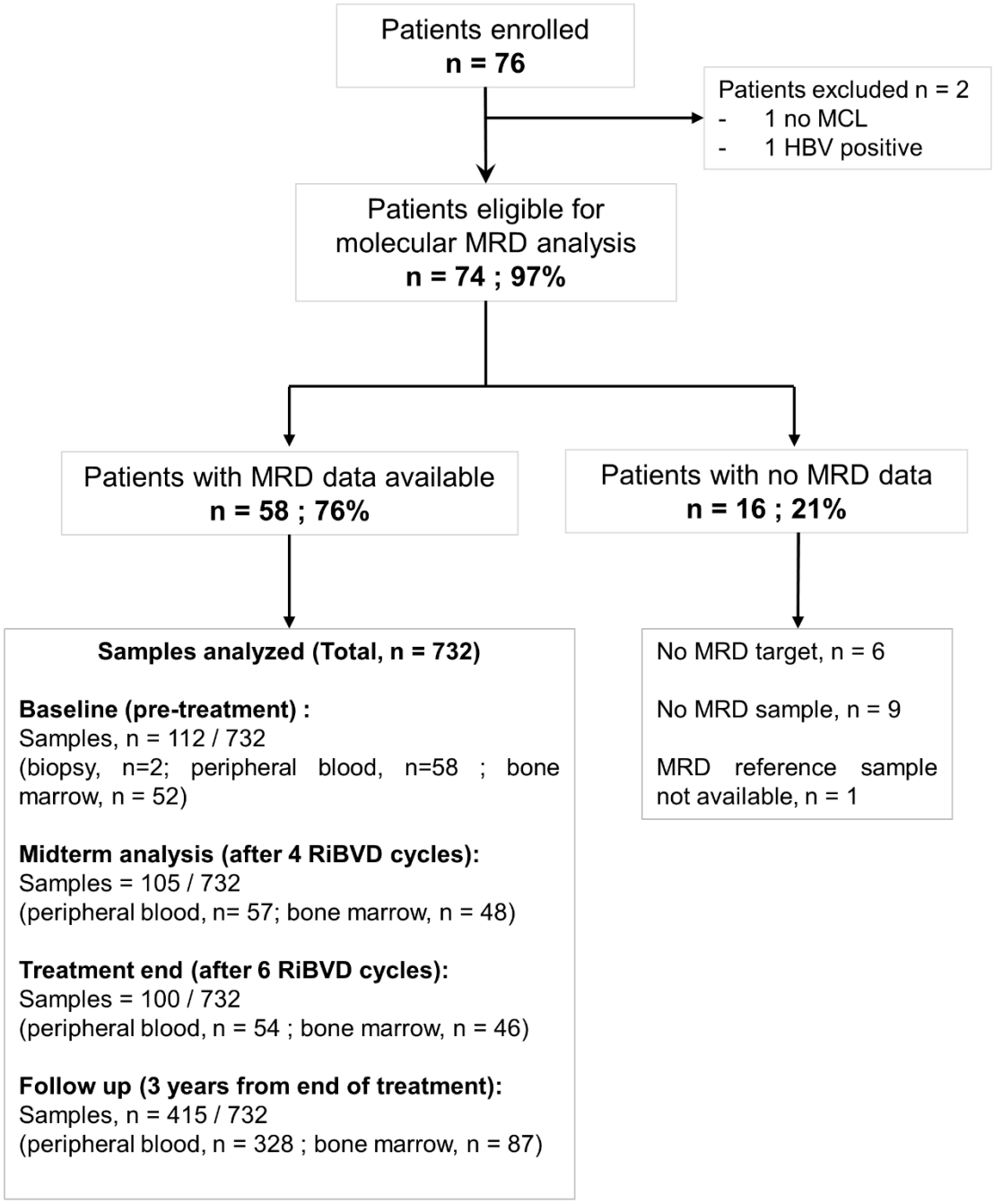
Stop**: Stop Bortezomib until recovery to a grade 0-1toxicity.

*~25% reduction of Bortezomib: reduction from 1.3 to 1.0 mg/m^2/dose or from 1.0 to 0.7 mg/m^2/dose.

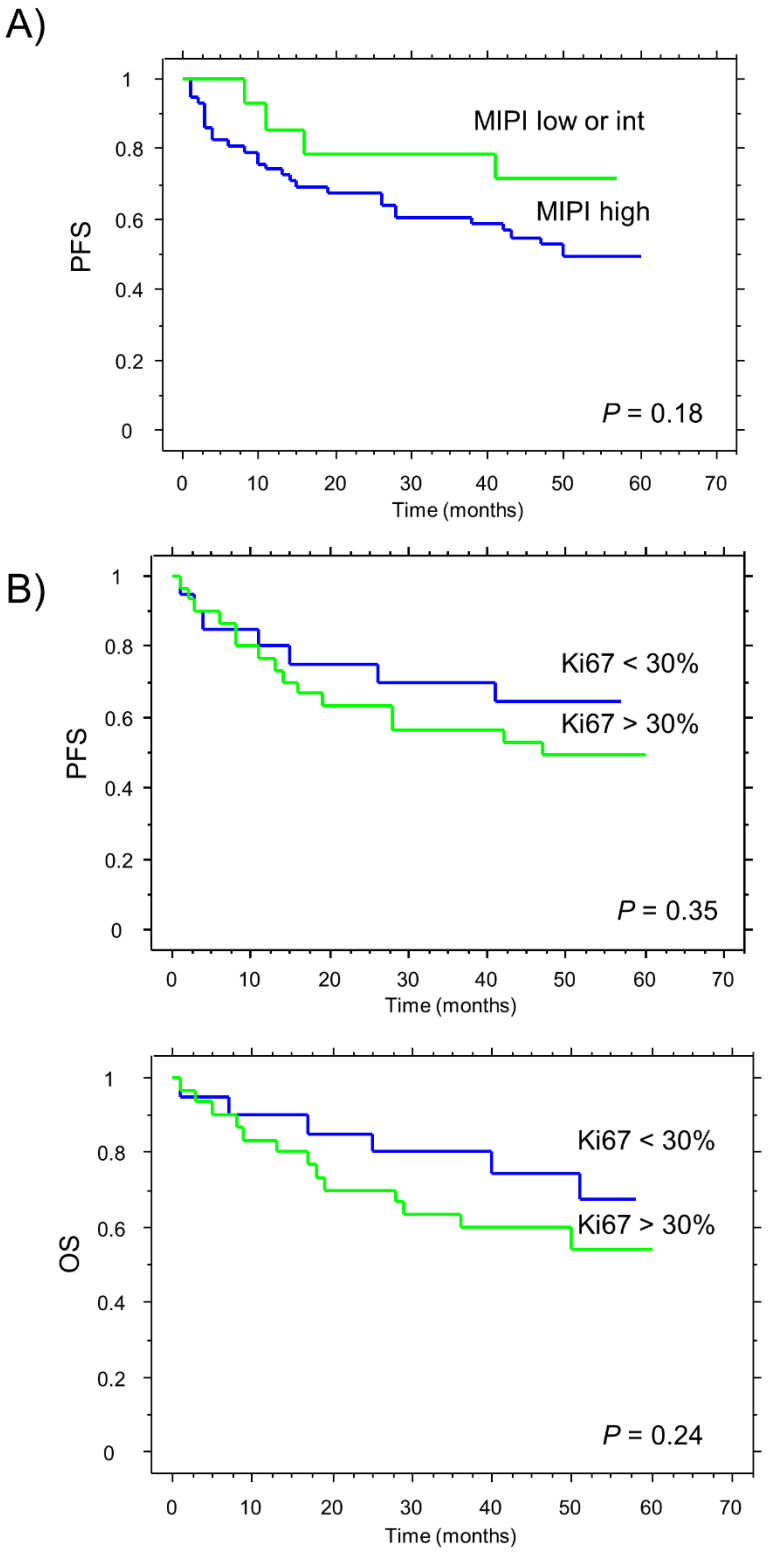
**~50% reduction of Bortezomib: reduction from 1.3 to 0.7 mg/m^2/dose.

Modifications at D4, D8, and D11 of each cycle

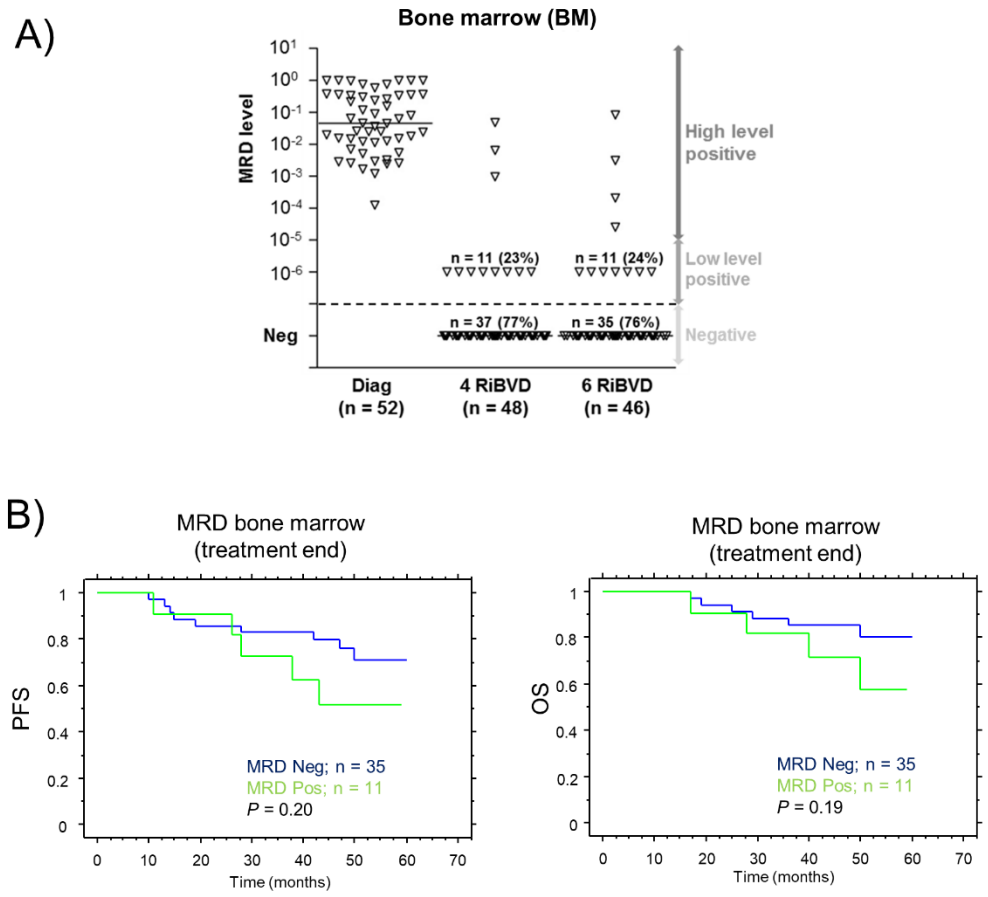
The dose of Bortezomib at D1 was the same at D4, D8 and D11, if neutrophils and platelets were >0.75 G/L and > 0 G/L, respectively at D4, D8 and D11; if not, bortezomib was not administered. GCSF was started until neutrophils recovery >1 G/L.



Supplementary Figure S1. MRD study cohort, sample numbers and type and work flow for the RiBVD phase 2 trial in elderly mantle cell lymphoma patients.



Supplementary Figure S2. Survival according to MIPI index and Ki67 staining. (A) PFS according to MIPI score, as indicated. (B) PFS (upper panel) and OS (lower panel) according to Ki67 status (cut-off of 30% positive cells).



Supplemental Figure 3. MRD responses and survival according to MRD status in the bone marrow in MCL patients treated in the RiBVD phase 2 study. **(A)** MRD levels in the bone marrow of patients treated in the RiBVD phase 2 study, as indicated. **(B)** Progression free (left panel) or overall survival of MCL patients treated in the RiBVD phase 2 study, as indicated.